

Thyroid hormone dysfunction in Chronic Renal Failure



Dissertation submitted in partial fulfillment of regulation for the award of M.D.
Degree in General Medicine (Branch I)



**The Tamilnadu
Dr. M.G.R. Medical University**
Chennai
March 2009

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Coimbatore Medical College & Hospital
Coimbatore - 641 014

certificate

*This is to certify that the dissertation entitled “**Thyroid hormone dysfunction in Chronic Renal Failure**”, herewith submitted by **Dr.B.KANNAN**, post graduate in General Medicine Coimbatore Medical College Hospital is the record of a bonafide research work carried out by him under our guidance and supervision from July 2006 to June 2008.*

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I solemnly declare that the dissertation titled “**Thyroid hormone dysfunction in Chronic Renal Failure**” was done by me at Coimbatore Medical College hospital from July 2006 to June 2008 under the guidance and supervision of **Prof Dr. VEERAKESARI.MD.** Unit Chief, Medical Unit VI.

This dissertation is submitted to the Tamilnadu Dr. MGR Medical University towards the partial fulfillment of the requirement for the award of MD Degree in General Medicine (Branch I).

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Dissertation Topic : THYROID HORMONE DYSFUNCTION
IN CHRONIC RENAL FAILURE

The Ethics Committee, Coimbatore Medical College has decided to inform that your Dissertation is accepted / ~~Not accepted~~ and you are permitted / ~~Not Permitted~~ to proceed with the above Study.

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INTRODUCTION

Chronic renal failure is a clinical syndrome due to irreversible renal dysfunction leading to excretory, metabolic failure culminating in accumulation of non protein nitrogenous substances and present with clinical manifestations.

Despite various etiologies, CRF is the final common pathway of irreversible destruction of nephrons ultimately resulting in alteration of all systems in the body. Kidney is closely related to thyroid in the fact that it is the only other organ that competes with iodide clearance.

Patients with CRF have many signs and symptoms suggestive of thyroid dysfunction like shallow complexion, edema, dry skin, cold intolerance, decreased BMR, asthenia and hyporeflexia. So in cases of CRF, it is difficult to exclude thyroid dysfunction on mere clinical background.

Various studies have been conducted on thyroid function in CRF patients, since the beginning, the results were inconsistent. Hyperthyroidism, hypothyroidism and euthyroidism all have been reported. The relation between thyroid dysfunction and severity of CRF is not clear. Several studies depict conflicting results both positive and negative.

Prevalence of hypothyroidism in end stage renal disease have been estimated between 0 and 9%. There is also increased prevalence of goiter in patients with ESRD.

In view of variability of thyroid function test in patients with CRF in previous studies, a prospective clinical and biochemical study on thyroid function in CRF

patients in Department of Nephrology, Coimbatore medical college hospital, Coimbatore
has been taken.

AIM OF THE STUDY

1. To study the prevalence of thyroid hormone dysfunction in patients with chronic renal failure.
2. To study the correlation between thyroid hormone dysfunction and severity of renal diseases.
3. To differentiate primary thyroid diseases from thyroid dysfunction due to chronic renal failure.

REVIEW OF LITERATURE

1. PHYSIOLOGY OF THYROID HORMONES

Thyroxine (T_4) and Triiodothyronine (T_3) are the principle hormones produced by thyroid gland.

Initially iodine is absorbed in the gut and converted to iodide and transported in the blood. It is then actively transferred into the thyroid cell by “**Iodide trapping**”. The trapped iodide is “**Oxidized**” to iodine and combines with tyrosine to form Mono iodotyrosine (MIT) and Diiodotyrosine (DIT). MIT and DIT are coupled to form T_3 whereas two DIT coupled to form T_4 . Oxidation, Iodination and coupling reactions are catalyzed by “**Thyroid peroxidase**”. Thyroid hormone thus produced are bound with thyroglobulin until secreted. (Pic.1)

It is secreted in the blood and transported in two forms. One is bound form, in which T_3 and T_4 are bound to plasma proteins namely thyroid binding globulin, prealbumin and albumin. T_4 is predominantly bound to thyroid binding globulin whereas T_3 is predominantly bound to albumin. The other form is free T_3 and T_4 . These free forms are in equilibrium with bound form.

In the periphery one third of T_4 is converted to T_3 by **5' Deiodenase** and 45% to rT_3 by **5 deiodenase**. They are further metabolized to Diiodothyronines. Only about 13% of T_3 is produced from thyroid gland and remaining 87% is formed from T_4 .

Control of thyroid hormones

The thyroid stimulating hormone (TSH) controls the secretion of T_3 and T_4 . It is secreted in pulsatile manner with peak secretion at night by anterior pituitary. TSH

secretion is stimulated by thyrotropin releasing hormone (TRH) which is secreted by hypothalamus. Both TRH and TSH release are under negative feedback of free T_3 and T_4 . (Pic.2)

Hypothyroidism

Hypothyroidism is a clinical syndrome caused by decreased level of thyroid hormones. It can be **primary** in which there is intrinsic disorder of thyroid gland or it may be **secondary** in which there is pituitary or hypothalamic defect.

Florid hypothyroidism can be diagnosed clinically. The **symptoms** of hypothyroidism in descending order of frequency are:

- Tiredness, weakness
- Dry Skin
- Feeling Cold
- Hair Loss
- Difficulty in concentrating and poor memory
- Constipation
- Weight gain with poor appetite
- Dyspnea
- Hoarseness of voice
- Menorrhagia (Later amenorrhea)
- Paraesthesia
- Impaired hearing

The *signs* of hypothyroidism in descending order of frequency are as follows:

- ❖ Dry coarse skin
- ❖ Cool peripheral extremities
- ❖ Puffy face, hands and feet (myxedema)
- ❖ Diffuse alopecia
- ❖ Bradycardia
- ❖ Peripheral edema
- ❖ Delayed relaxation of ankle jerk
- ❖ Carpal tunnel syndrome
- ❖ Serous cavity effusions

In biochemical studies, TSH is the single most important parameter for screening hypothyroidism. A normal TSH level rules out primary hypothyroidism but not secondary. To diagnose primary hypothyroidism TSH level should be above 20 $\mu\text{IU/ml}$ or at least above 10 $\mu\text{IU/ml}$ if clinical features strongly suggest.

In the presence of elevated TSH, low T_4 especially free T_4 is necessary to confirm hypothyroidism. Circulating free T_3 is usually reduced. But it may be normal in 25% of hypothyroid patients. So, T_3 measurements are not reliable indicators of hypothyroidism.

Hyperthyroidism

Hyperthyroidism is a clinical syndrome which results from exposure of the body tissues to excess circulating levels of free thyroid hormones.

The **symptoms** of hyperthyroidism in descending order of frequency are as follows.

- ❖ Hyper activity, irritability
- ❖ Heat intolerance and sweating
- ❖ Palpitations
- ❖ Fatigue and weakness
- ❖ Weight Loss with increased appetite
- ❖ Diarrhoea
- ❖ Oligomenorrhea, loss of libido

The **signs** of hyperthyroidism in descending order of frequency are as follows:-

- ❖ Tachycardia. atrial fibrillation
- ❖ Tremor
- ❖ Goiter
- ❖ Warm, moist skin
- ❖ Muscle weakness, proximal myopathy
- ❖ Lid retraction or lag
- ❖ Gynaecomastia

Laboratory investigation shows TSH below normal level. Free and total thyroid hormone levels are increased.

In 2 to 5% of patients, only T_3 is increased, a condition called “ **T_3 thyrotoxicosis**”. Occasionally, total and free T_4 will be increased with normal T_3 level. This condition is called “ **T_4 thyrotoxicosis**”.

NON THYROIDAL ILLNESS^{6,9,23,40,48,53}

Alteration in serum thyroid hormone occurs in wide variety of illness which predominantly affect the T_3 level in whom no intrinsic diseases of thyroid gland is detected. It was variously termed as “**Low T_3 syndrome**”, “**Sick euthyroid syndrome**”, “**Non thyroid illness syndrome**” and “**Thyroid hormone adaptation syndrome**”.

This syndrome occurs in wide variety of illness as follows.

- i. Acute critical illness and febrile illness such as infection, myocardial infarction, etc.,
- ii. Injuries such as burns, trauma, etc.,
- iii. Surgery
- iv. Fasting
- v. Diabetes Mellitus
- vi. Liver disease
- vii. Renal disease
- viii. Ketogenic diet
- ix. Drugs such as Glucocorticoids, dopamine, phenytoin and Beta Blocker
- x. Malignancy
- xi. Psychiatric illness

In non thyroid illness state, initially there is decrease in serum T_3 level, both total and Free T_3 (FT₃). This is associated with increase in reverse T_3 (rT₃).

As illness progresses, there is decrease in serum T_4 also, a state called “**low T_3 , T_4 State**”. Although total T_4 level decreases, the free T_4 (FT₄) remains normal or slightly reduced. In spite of this reduced T_3 and T_4 level, serum TSH level remains normal or reduced by which it is differentiated from primary hypothyroidism. But many studies have shown slight elevation of TSH level in non thyroidal illness in the absence of hypothyroidism^{7,24,29}.

CHRONIC RENAL FAILURE

Pathophysiology

The unique property of kidney is that in the presence of CRF, compensatory and adaptive mechanism maintain acceptable health until the GFR is above 10 to 15 ml/min and life sustaining renal excretory and homeostatic function continues until the GFR is less than 5ml/min.

Intact nephron hypothesis

The explanation proposed for these adaptive mechanism is that in CRF there is progressive loss of nephrons, so most of the nephrons are non functioning. The remaining few functioning nephrons tend to hypertrophy and take an increased work load so that overall loss of function is minimized. This indicates that GFR of the individual functioning nephrons has increases above normal, a state known as **hyperfiltration**. This increase in single nephron GFR in functioning nephrons produce an increased volume of filtrate and their tubules respond appropriately by excreting fluids and solutes in amounts which maintain external balance. This is due to close

integration of glomerular and tubular functions called “glomerulotubular balance” preserved until terminal stages of CRF. These above stated popular explanation for continuing function in remaining nephrons, is the “intact – nephron hypothesis”.

Trade Off Hypothesis

It is described that adaptation arising in CRF may control one abnormality, but only in such a way as to produce other changes characteristic of uraemic syndrome. The mechanism involved is unknown. This trade off hypothesis is described in hormones like parathormone, vasopressin and ANP, solutes like sodium, potassium, phosphate and others.

Uraemic Syndrome

Uraemic syndrome is a consequence of combination of the effects of the retention of waste products in all organ system and the failure of both endocrine and homeostatic function of kidney.

The potential toxic substances that accumulate include purine metabolites amines indoles, phenols, myoinositol and acid polyols.

“**Middle molecules**” are nitrogenous substances of molecular weight between 50 and 5000 da. They are also suspected of contributing to uraemia.

Electrolyte and metabolic changes

Hyperkalemia usually develops when GFR falls to less than 20-25 mL/min because of the decreased ability of the kidneys to excrete potassium. It can be observed sooner in patients who ingest a potassium-rich diet or if serum aldosterone levels are low, such as in type IV renal tubular acidosis, hyperkalemia in CKD can be aggravated by an extracellular shift of potassium, such as that occurs in the setting of acidemia or from lack of insulin.

Metabolic acidosis often is mixed, non-anion gap and anion gap, the latter observed generally with CKD stage 5 but with the anion gap generally not higher than 20 mEq/L. In CKD, the kidneys are unable to produce enough ammonia in the proximal tubules to excrete the endogenous acid into the urine in the form of ammonium. In CKD stage 5, accumulation of phosphates, sulphates, and other organic anions are the cause of the small anion gap.

Extracellular volume expansion and total-body volume overload results from failure of sodium and free water excretion. This generally becomes clinically manifest when GFR falls to less than 10-15 mL/min, when compensatory mechanisms have become exhausted. Patients present with peripheral and, not uncommonly, pulmonary edema and hypertension. At a higher GFR, excess sodium and water intake could result in a similar picture if the ingested amounts of sodium and water exceed the available potential for compensatory excretion.

Hematological changes

Normochromic normocytic anemia principally develops from decreased renal synthesis of erythropoietin, the hormone responsible for bone marrow stimulation for red blood cell (RBC) production. It becomes more severe as GFR progressively decreases with the availability of less viable renal mass. No reticulocyte response occurs. RBC survival is decreased and tendency of bleeding is increased from the uremia-induced platelet dysfunction

Bone changes

Secondary hyperparathyroidism develops because of hypocalcemia, decreased renal synthesis of 1,25-dihydroxycholecalciferol (1,25-dihydroxyvitamin D, or calcitriol), and hyperphosphatemia.

If serum levels of PTH remain elevated, a high-bone turnover lesion, known as osteitis fibrosa cystica develops. This is known as renal osteodystrophy. These lesions develop in patients with severe CKD and are common in those with ESRD. Osteomalacia and adynamic bone disease are the two other lesions observed. The former, observed primarily from aluminum accumulation, is markedly less common than the latter, whose etiology is unclear. Adynamic bone disease represents the predominant bone lesion in patients on chronic peritoneal dialysis and is increasing in frequency. Dialysis-related amyloidosis from beta2-microglobulin accumulation in patients who have required chronic dialysis for at least 8-10 years is another form of bone disease that manifests with cysts at the ends of long bones.

OTHER CHANGES

- * Pericarditis - Can complicate with cardiac tamponade, possibly resulting in death.
- * Encephalopathy - Can progress to coma and death.
- * Peripheral neuropathy.
- * Restless leg syndrome.
- * GI symptoms - Anorexia, nausea, vomiting, diarrhea.
- * Skin manifestations - Dry skin, pruritus, ecchymosis.

- * Fatigue, increased somnolence, failure to thrive.
- * Malnutrition.
- * Erectile dysfunction, decreased libido, amenorrhea .
- * Platelet dysfunction with tendency to bleeding.

Chronic renal failure as non thyroidal illness

Chronic renal failure is one among the condition causing low T₃ syndrome. These are the some of the condition having low T3 syndrome.

TABLE - B

**CHANGES IN SERUM THYROID HORMONES AND TSH CONCENTRATION
IN PATIENTS WITH NON THYROIDAL ILLNESS**

Conditions	Serum T₃	Serum rT₃	Serum T₄	Serum Free T₄	Serum TSH
Fasting	↓	↑	=	=	↓
Mild illness	↓	↑	=	=, ↑	=
Critical illness	↓	↑	↓	=, ↓	↓
Surgical trauma, burns	↓	↑	↓	↓	=, ↓
Chronic renal failure	↓	=	=, ↓	=, ↓	=, ↓
Hepatitis	=, ↑	=, ↑	=, ↑	=, ↓	=
HIV infection	=	↓	=	=, ↓	=, ↑
Depression	=, ↓	=, ↑	=, ↑	=, ↑	=, ↓

= No change, ↓ Decreased, ↑ Increased

Chronic renal failure has been divided into five stages based on the endogenous Creatinine clearance. A typical patient with chronic progressive renal diseases may be considered to pass through all 5 stages.

Stage - I : (Decreased renal reserve)

Endogenous Creatinine clearance is more than 90 ml/min.

Stage - II : (Mild renal insufficiency)

Creatinine clearance is 60-89 ml/min. Serum Creatinine range from 2-4 mg/dl. Symptoms of mild azotemia, inability to concentrate urine, leading to polyuria and hypovolemia may be the presenting features.

Stage - III : (Moderate renal failure)

Creatinine clearance is less than 30- 59ml/min. This stage may manifest with anaemia, hypertension, hyperphosphatemia, pruritis, poor intellectual performance and acidosis.

Stage - IV : (Severe renal failaure)

Creatinine clearance is 15-29 ml/min. Clinical manifestations are similar to Stage III.

Stage - V : (End stage renal disease)

End stage renal disease is reached at glomerular filtration rate (GFR) of 15 ml/min. The clinical manifestations are pulmonary odema, pericarditis, hyperkalemia, fits and death. Usually serum creatinine is over 8 – 10 mg/dl.

As with other low T_3 syndromes, CRF produces decrease in T_3 when GFR falls below 50%. There is marked decrease of T_3 than T_4 as the GFR decreases. In ESRD, on average, diminished T_4 is found in 29% of the patients and diminished T_3 in 55% of the patients.

CRF as low T_3 syndrome differs from other conditions causing similar illness, by two unique features⁴⁰.

- * rT_3 is usually low or normal in CRF due to redistribution into the extra vascular compartment.
- * Increased incidence of goiter is present in CRF, probably due to decreased clearance of iodine by the kidney.

PATHOPHYSIOLOGY OF LOW T_3 SYNDROME

As stated above in CRF there is initial decrease in total T_3 , later T_4 in spite of normal or low TSH. Various mechanism has been proposed for the change in Thyroid profile.

According to the postulates, CRF affect thyroid economy at all levels as follows.

A. Changes in Hypothalamic – pituitary – thyroid axis

- i. Sensitivity of TSH secretion to low thyroid hormone is decreased.
- ii. Limited TSH reserve⁴⁰
- iii. Due to changes in thyrotrophs or to decreased TRH secretion, as manifested by decrease in nocturnal pulses of TSH secretion^{2,17,53}.
- iv. Tissue concentration of the hormone may be appropriate for the patient, so the patient is in euthyroid state⁴⁰.
- v. Serum FT_3 and FT_4 appears normal by sensitive methods^{3,5}.

B. Changes in hormone Transport

- i. Presence of protein and non protein inhibitors preventing the binding of thyroxine with thyroxine binding protein. Non protein inhibitor is non esterified unsaturated fatty acid^{22,53}.
- ii. Acquired intrinsic structural alternation in the T_4 binding site²³.
- iii. Decrease in concentration of thyroxine binding globulin^{40,53}

C. Changes in metabolism

- i. Decrease in the activity of Iodothyronine 5 – Deiodinase leading to low T_3 ^{40,53}

- ii. Increase in Non-deiodinative pathways of iodothyronine degradation leading to increased serum T_3 sulphate, diiodotyrosine, triiodo thyroacetic acid and tetraiodothyroacetic acid^{40,53}.

As previously stated, there is no increase in rT_3 in CRF due to redistribution of rT_3 into extra vascular compartment^{40,53}.

D. Changes in plasma membrane Transport

T_3 and T_4 may enter cells not only by diffusion but also by active energy dependent transport across plasma membrane.

Accumulation of the following substances prevents uptake and subsequent deiodination.

- a. 3 – carboxy 4 – methyl 5 – propyl 2 – Furane (CMPF)
- b. Indoxyl sulphate

In uraemia the action of thyroid hormones at nuclear level are not compromised. Recent study showed increased receptor expression to preserve tissue Euthyroidism⁵².

DIAGNOSIS OF PRIMARY THYROID DISEASES IN CRF

Recent studies have shown the prevalence of hypothyroidism is increased in chronic renal failure, and also several clinical features of both hypothyroidism and chronic renal failure are similar, so differentiating both the conditions on clinical background is less likely. Hence, all the CRF patients with symptoms of hypothyroidism should be screened for hypothyroidism.

Hypothyroidism should be diagnosed only if the following prevails.

- a. Basal TSH level should be elevated more than 20 μ IU/ml.
- b. Both total and free T_4 are distinctly low in the presence of normal TBG³⁵.
- c. Presence of anti thyroid antibodies can provide clue for hypothyroidism³⁵.
- d. rT_3 is not useful because it is decreased in CRF.

Primary hyperthyroidism is very rare in CRF. This condition is diagnosed by

- a. Low serum TSH
- b. High serum total and free T_4 concentration.

High serum T_4 with low T_3 in the presence of CRF should make the possibility of T_4 thyrotoxicosis. This is because serum T_3 level will be suppressed in low T_3 syndrome with serum T_4 unaffected⁵³.

MANAGEMENT

Several studies have been conducted in patients with the T_3 syndrome in order to correct the thyroid profile by treating with L-Thyroxine¹⁸ and Triiodothyronine⁵.

Gregory Brent et al¹⁸ conducted study in non thyroidal illness patients by treating all the patients with serum total T₄ less than 5 µg/dl with 1.5 µg/Kg of L-thyroxine for 2 weeks. Thyroxine level increased significantly in treated patients. Serum T₃ levels were also raised. But mortality was increased in treatment group on day 5 – 17.

Carter et al⁵ studied effects of Triiodothyronine administration in patients with chronic renal failure. Study showed serum T₃ level did not change over a period of 12 weeks. But the mean serum T₄ and TSH levels were affected significantly. There was no subjective improvement in these patients.

Based on this observation, it has been suggested that low serum T₃ level in patients with severe renal failure is metabolically protective and it is interpreted as physiological adaptation to reduce basal metabolic rate (BMR) and to conserve energy in an adverse environment. Hence, this condition has been renamed as **“Thyroid hormone adaptation syndrome”**⁵³.

Administration of T₄ or T₃ causes suppression of TSH and increases the catabolism. So, administration of thyroid hormone is not beneficial. Study also showed increased mortality with the treatment. Therefore, thyroid hormone should not be given in CRF unless true hypothyroidism can be documented.

PROGNOSIS

Magnitude of the Thyroid dysfunction that occurs in patients with chronic renal failure, in general, reflects the severity of the illness. The prognosis is poor in patients with lower serum T₃ and T₄ or TSH concentration. Studies have shown that after renal transplant the low T₃, T₄ and TSH return to normal level.

MATERIALS AND METHODS

Patients admitted to the Nephrology ward, Coimbatore Medical College Hospital, Coimbatore with chronic renal failure who are on conservative management.

Study Design:

Single Centre, Non randomized prospective study.

Study Period:

Study was conducted between January 2007 and August 2008 for a period of 18 months.

Sample Size:

In the study period of 18 months among patients admitted in Nephrology ward after applying inclusion and exclusion criteria 50 patients will be included in this study.

Patients who fulfill the criteria for CRF and who are on conservative management, Thyroid profile would be done in all patients who fulfilling the criteria. Informed consent was obtained from all patients.

Selection Criteria:

1. Symptoms of uraemia for 3 months or more.
2. Elevated blood urea, Serum creatinine
3. Ultrasound evidence of chronic renal failure
 - a. Bilateral contracted kidneys- size less than 8 cm in male and size less than 7 cms in female
 - b. Poor corticomedullary differentiation

- c . Type 2 or 3 renal parenchymal changes
- 4. Supportive laboratory evidence of CRF like anemia, urine specific gravity, changes in serum electrolytes, etc.,

Exclusion Criteria:

- 1. Patients underwent peritoneal dialysis or hemodialysis
- 2. Nephrotic range of proteinuria
- 3. Low serum protein especially albumin
- 4. Other conditions like
 - a. Acute illness
 - b. Recent surgery, trauma or burns
 - c. Diabetes mellitus
 - d. Liver diseases
 - e. Drugs altering thyroid profile like amiodarone, steroids, dopamine, phenytoin, oestrogen pills, iodine containing drugs.

Detailed clinical history and clinical examination was undertaken with preference to thyroid and renal diseases. The following investigations were performed.

- 1. Urine for specific gravity and broad cast
- 2. Peripheral smear for anaemia and burr cells.
- 3. Renal parameters like blood urea, Serum creatinine and Creatinine clearance (using Cockcroft- Gault formula)
- 4. Serum calcium and phosphorus

5. Serum cholesterol for hypothyroidism
6. 24 hours urine protein and serum protein to rule out nephrotic syndrome and hypoproteinemia respectively
7. ECG and chest X ray to look for features for hypothyroidism and renal failure like pleural effusion, pericardial effusion.
8. USG abdomen for evidence of chronic renal failure

After selecting the patients, fulfilling the above criteria, about 5ml of blood sample is collected in non heparinised serum bottle and sent for thyroid profile.

Components of thyroid profile in this study are serum triiodothyronine, serum thyroxine, serum thyroid stimulating hormone. Quantitative determination of T3, T4, TSH is done by Enzyme linked Immunosorbent Assay.

RESULTS AND OBSERVATIONS

50 patients with CRF who were on conservative management were studied. Among 50 patients, 10 patients were female and 40 patients were male. The age varied from 12 – 70 years. Among 50 patients, 10 patients were 30 years and below, 33 patients were in the age group of 30 – 60 years and 7 patients above 60 years.

Observation regarding CRF in this study

The duration of CRF in this study varied from 3 months to 5 years. The Creatinine clearance varied from 6 ml/min to 34 ml/min. 20 patients had GFR 10 ml/min accounting for 40%, 20 patients GFR 11 – 20 ml/min accounting for another 40%, remaining 10 patients accounting for 20% had GFR more than 20 ml/min.

Blood urea varied from 64 to 170 mg/dl and Creatinine varied from 3 mg to 17.2 mg/dl.

24 hours urinary protein excretion was less than 1 gm/day in all the patients in this study group.

Serum calcium and phosphorous were normal in all the patients. 80% of the patients had anaemia with peripheral smear revealing normocytic normochromic anaemia in 72% and hypochromic anaemia in 8% of the patients.

TABLE - 1**SERUM CONCENTRATION OF THYROID HORMONE**

Thyroid hormones	Normal range	Study range	Mean	Std. Dev.	Mean excluding hypothyroidism	Std. Dev
Serum T ₃ ng/ml	0.6 – 2.1	0.2 to 2	0.673	0.414	0.7122	0.4368
Serum T ₄ µg/dl	5 – 13	0.5 to 9.5	5.622	2.27	5.99	2.08
Serum TSH µIU/ml	0.4 – 7	0.6 to 27	6.53	6.98	4.75	4.151

TABLE - 2

DISTRIBUTION OF LOW T₃ AND T₄ AMONG VARIOUS

LEVELS OF TSH

TSH level μ IU/ml	No. of Patients	No. of Patients
	with Low T₃	with Low T₄
≤ 7	16 (57.14%)	8 (53.33%)
7.1 – 20	7 (25%)	2 (13.33%)
> 20	5 (17.85%)	5 (33.33%)

DISTRIBUTION OF LOW T3 AND T4 AMONG VARIOUS LEVELS OF TSH

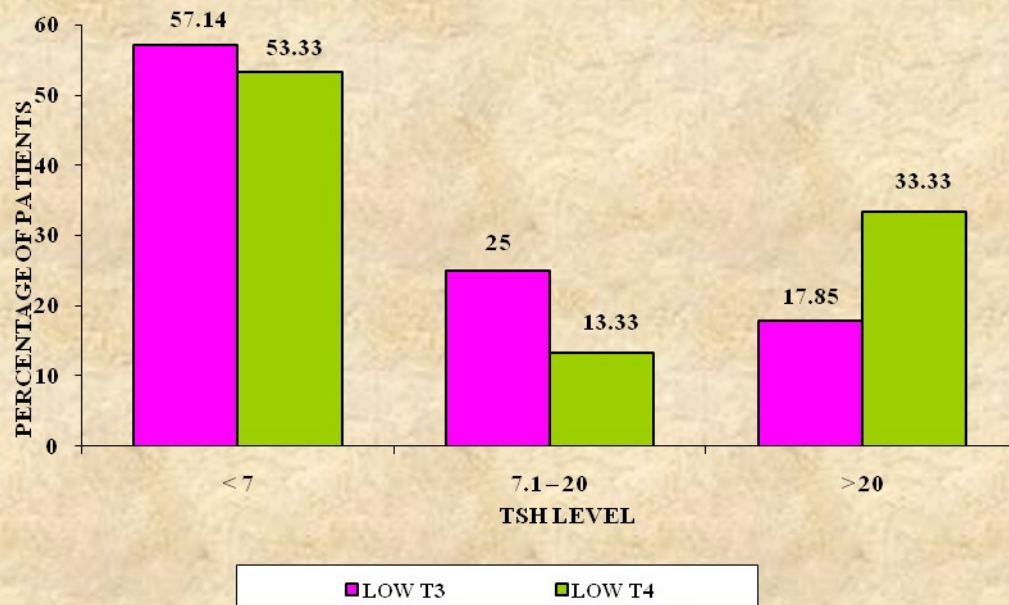
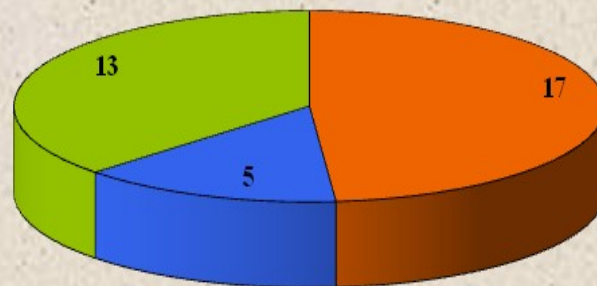


TABLE - 3

ANALYSIS OF THYROID DYSFUNCTION IN THIS STUDY

Thyroid dysfunction	No. of Patients	Percentage
Low T ₃ syndrome	23	46%
Low T ₄ syndrome	10	20%
Hypothyroidism	5	10%

DISTRIBUTION OF THYROID PROFILE IN OUR STUDY



■ Low T3 Syndrome (n=23)

■ Hypothyroidism (n=5)

■ CRF without thyroid dysfunction (n=22)

Ultra sound abdomen showed evidence of CRF in all patients contracted kidney was present in 90% of the patients. Remaining patients had poor corticomedullary differentiation.

Among the 50 patients, low serum T_3 level was found in 28 patients (56%), 5 patients among the low serum T_3 level also had high TSH value more than 20 μ IU/ml with low T_4 level and also symptoms suggestive of hypothyroidism.

These patients as per the criteria were grouped under “primary hypothyroidism”. Remaining 6 patients had slightly elevated TSH ranging between 9 and 14 μ IU/ml. In these 6 patients, only 3 patients had low T_3 level, among which only one patient had few clinical features of hypothyroidism. So, these 6 patients didn’t satisfy the criteria for hypothyroidism fully. So all 23 patients were grouped under “Low T_3 syndrome” of “sick Euthyroid syndrome”.

TABLE - 4**ANALYSIS OF SERUM T₃ T₄ AND TSH EXCLUDING
HYPOTHYROIDISM**

Thyroid d y s f u n c t i o n	No. of Patients with Normal values	%	No. of Pt with low values	%	No. of pt with high values	%
T ₃	22	44%	23	46%	NIL	NIL
T ₄	35	70%	10	20%	NIL	NIL
TSH	38	76%	NIL	NIL	7	14%

TABLE - 5

AGE INCIDENCE OF LOW T₃ SYNDROME IN THIS STUDY

Age in years	No. of Patients	Low T₃ syndrome	Percentage
≤ 30	10	3	33%
31 – 60	33	17	51.50%
> 60	7	3	42.85%

AGE INCIDENCE OF LOW T3 SYNDROME IN THIS STUDY

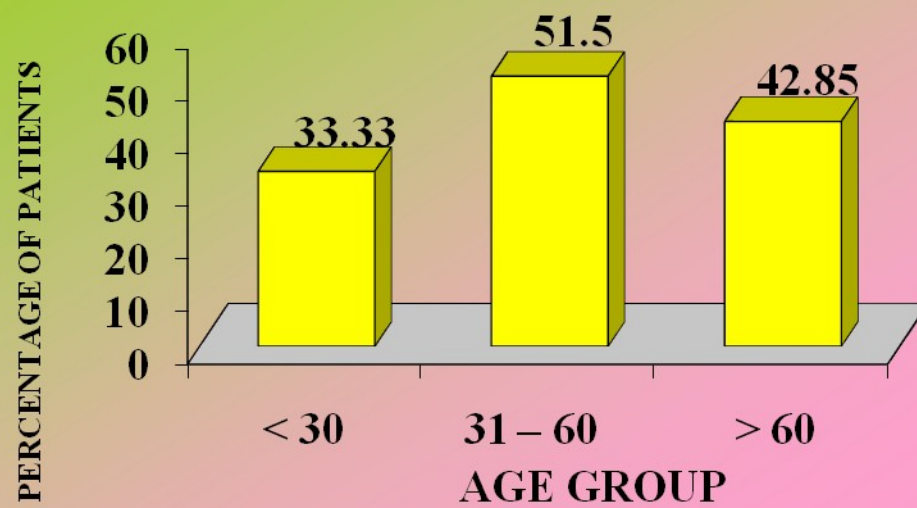


TABLE - 6

SEX INCIDENCE OF LOW T₃ SYNDROME IN THIS STUDY

Sex	NO. OF PATIENTS	Low T₃ Syndrome	Percentage
Male	40 (80%)	20	50%
Female	10 (20%)	3	30%



Dry, flaky skin was present in 15 patients of which only 4 patients were hypothyroid.

Sinus bradycardia was present in 7 patients.

Hypothyroidism didn't show any linear correlation with GFR. Increased number of hypothyroid patients of about 4 in number were present in GFR 11 – 20 ml/min whereas only 2 patients had hypothyroidism in GFR less than 10 ml/min.

Age comparison of Low T_3 syndrome in table-5 shows about 30% of CRF patients below 30 years of age have low T_3 syndrome. The percentage increases to 51.51% in the age group 31 – 60 years. This is probably due to increased CRF patients in this age group. In age above 60 years, 42.85% have low T_3 syndrome.

Sex incidence in this study (Table-6) shows 50% of males have low T_3 syndrome and only 30% of the females have low T_4 syndrome.

Observation of T_3 in this study

T_3 level in this study varied from 0.2 to 2 ng/ml. The mean value of T_3 is 0.67 ng/ml (Table-1). Excluding the patients with primary hypothyroidism, the mean value is 0.71 ng/ml. This value was in low normal limit. Excluding hypothyroidism T_3 levels were studied in relation to GFR. It was found that mean value of serum T_3 is low (0.538 ng/ml) only in patients with GFR less than 10 ml/min (Table – 10). The mean value is low normal in patients with GFR more than 10 ml/min. According to the study, number of patients with low T_3 increase with increase in severity of the renal failure (Table-8) in spite of low T_3 levels.

Observations of T₄ in the study

Serum T₄ level in the study varies from 0.5 to 9.5 µg/dl. Mean value of serum T₄ among 50 patients 5.62 µg/dl Excluding hypothyroid patients, the mean value is 5.99 µg/dl. This value is within low normal level of T₄.

TABLE - 8**DISTRIBUTION OF LOW T₃ AND T₄ SYNDROME IN THIS STUDY**

Creatinine Clear ance ml/min	Low T₃ Syndrome		Low T₄ Syndrome	
	No. of Patient	Percentage	No. of	Percentage
≤ 10	13	65%	6	30%
11 – 20	7	35%	3	15%
> 20	5	30%	1	10%

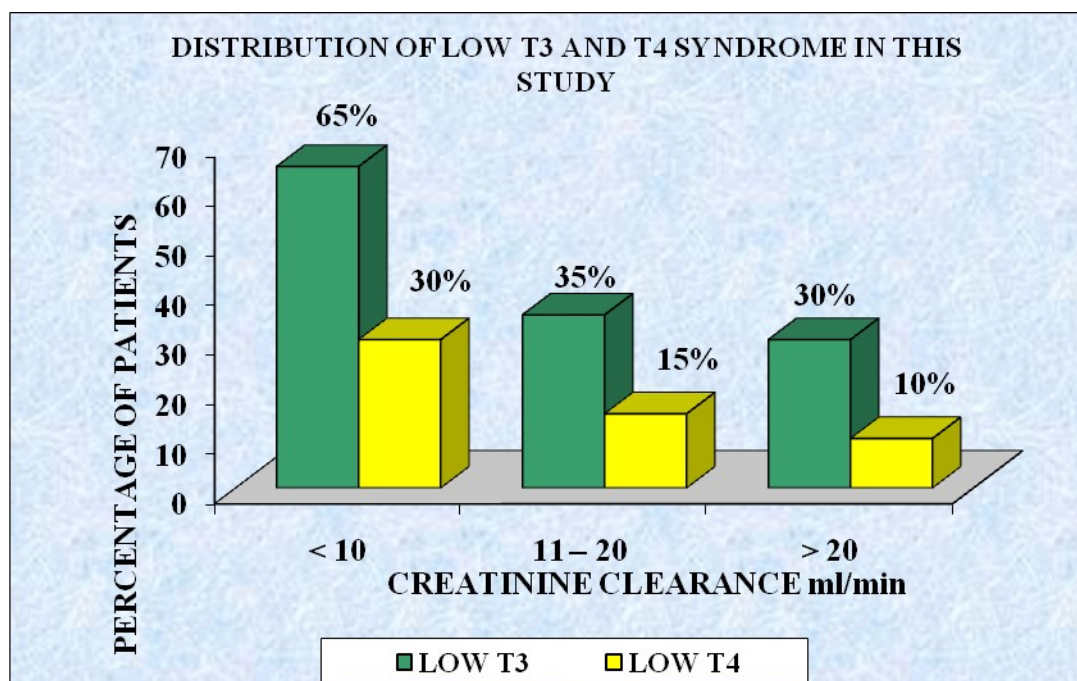


TABLE - 9

**DISTRIBUTION OF THYROID DYSFUNCTION IN THIS STUDY AMONG
VARIOUS CREATININE CLEARANCE LEVELS**

Creatinine Clearance ml/min	No. of Patients	Low T₃ Syndrome	Hypothyroidism
≤ 10	20 (40%)	13 (65%)	3 (15%)
11 – 20	20 (40%)	7 (35%)	2 (10%)
> 20	10 (20%)	3 (30%)	NIL

CORRELATION

SEVERITY OF RENAL DISEASE AND HYPOTHYROIDISM

Creatinine mg/dl	Mean T4 μg/dl	Mean T3 ng/dl	Mean TSH μIU/ml	Mean T4 μg/dl	Mean T3 ng/dl	Mean TSH μIU/ml
≤ 10 (n=17)	0.538	0.40	5.02	2.10	5.22	4.25
11 – 20 (n=18)	0.82	0.43	6.69	2.17	3.77	3.78
> 20	0.8	0.31	6.32	2.04	5.72	5.00

Excluding 5 hypothyroidism patients who have low T4 values, 9 (21.33%) other patients had T4 level below normal and low T3 syndrome.

Number of patients with low T4 does not correlate with severity of renal disease (Table 8). The mean value of T4 excluding hypothyroidism patients was normal at all the stages of renal failure (Table 9).

None of the patients had T4 value above normal level.

Observation of TSH in the study

Values of TSH vary from 0.6 to 27 μIU/ml with mean value in 6.53 μIU/ml.

Excluding hypothyroidism mean value is 4.75 μ IU/ml. This shows normal serum level of TSH.

Among the 50 patients, TSH was normal in 38 patients (76%) and values between 7.1 – 20 μ IU/ml in 7 patients (14%). It was elevated more than 20 μ IU/ml in 5 patients (10%).

According to our study, in patients with low T_3 syndrome, the mean values of TSH in various stages of renal failure are within normal range. But the values of TSH didn't show any linear correlation with GFR.

DISCUSSION

Thyroid dysfunction in CRF was extensively studied by **Ramirez**³⁷.

part from his study, various studies conducted in this line have showed different results.

In this study, patients only on conservative management were studied. This is because thyroid profile undergoes changes due to dialysis independent of that due to chronic renal failure. Dialysis also changes the previous serum status of thyroid hormone in the patients with renal failure. Many studies have conducted by comparing CRF patients conservative Management and Hemodialysis by **Ramirez**⁴² and **kayima et al**²⁹.

Many studies conducted in CRF patients showed low T₃ values. Low T₃ had been reported in **Ramirez et al**³⁷, **Hegedus et al**²¹, **Beckett et al**^{37,21,2} studies, that to in severe renal failure. **Ramirez and spectar et al**³⁷ study showed linear correlation between the mean serum T₃ and T₄ and severity of renal failure.

As with other studies, mean T₃ level in our study was reduced below normal in GFR less than 10 ml/min. In higher GFR, it was present in low normal and there was no linear correlation between T₃ level and GRF which is consistent with **Avasthi et al study**¹.

Mean T₄ level in this study is within normal limits in all levels of GFR, but it is in low normal level and also it does not correlate with the severity of renal failure.

In this study, not all the patients with CRF have low T₃ and T₄. It is estimated that only 58% (29 patients) of patients have Thyroid Profile abnormality. Remaining 42% of patients have normal thyroid profile.

Among 58% of these patients exclude primary hypothyroid patients 28% have only low T₃ level with normal T₄ level. Remaining 20% have both low T₃ and T₄ level. The percentage of patients having low T₃ and T₄ gradually increase, with decrease in GFR. The patient who will develop such change in thyroid profile is not known.

Excluding hypothyroidism, mean TSH level in our study is within normal limits. The mean TSH levels are also within normal limits for the various ranges of GFR. But TSH level doesn't show any linear correlation with the severity of renal failure. This is consistent with the study conducted by **Spector and Ramirez et al**^{49,37}. These studies demonstrated abnormality in hypophyseal mechanism of TSH release in uraemic patients as the as the TSH response to the TRH was blunted.

Other studies conducted by **Joseph et al and Hardy et al**^{24,19} revealed low T₃ T₄ level with high TSH level suggesting maintenance of pituitary thyroid axis.

In this study, excluding those with hypothyroidism, seven patients had mild elevation of TSH with low T₃ level. Among these patients, T₄ is within normal limits in 4 of the patients. In the remaining 3 patients T₄ is below normal. There were no clinical features suggestive of hypothyroidism in these patients. Investigations like FT₄, FT₃ TRH response and anti thyroid auto antibodies can be done to diagnose hypothyroidism in these patients.

Our study is consistent with the results of **Ramirez et al**³⁷ study showing low T₃, low T₄ and normal or mild elevation of TSH. Yet it is unclear that to what extent these changes are responsible for the manifestations of Uraemic syndrome. From the various studies it has been suggested that this thyroid profile derangements is a part of body adaptation mechanism.

Dialysis

As stated previously, Hemodialysis and continuous ambulatory peritoneal dialysis have shown to affect the thyroid profile independently of CRF. Also drugs like heparin, furosemide used during dialysis will affect the thyroid profile.

Kayima et al²⁹ and **Giordano et al**¹⁶ have conducted studies regarding effect of dialysis on CRF patients with thyroid dysfunction. These study showed no significant improvement in thyroid profile after repeated hemodialysis.

But in the patients who have undergone renal transplant surgery, most of the thyroid function parameters returned to normal with TSH below normal⁵⁵.

Hypothyroidism

Previous studies by **Quion verde et al**³⁶ reported high prevalence of hypothyroidism in CRF. It was estimated to be about 5% in patients with terminal renal failure.

Detail study by **Kaptein et al**^{25,26} estimated the prevalence of primary hypothyroidism was about 2.5 times much frequent in chronic renal failure and dialysis. The hypothyroidism in CRF was estimated to range between 0 and 9.5% Kaptein study also estimated the presence of anti thyroid antibody titer in 6.7% of CRF.

In our study, the hypothyroidism is present in 10% of the patients but doesn't correlate with the severity of the renal failure. The symptoms of hypothyroidism were distributed equally in both hypothyroid and CRF patients in our study. Signs of hypothyroidism were more common in CRF without hypothyroidism than with hypothyroidism.

So, diagnosis of hypothyroidism in CRF mainly rest on TSH level which should be very high (> 20 MIU/dl) with low serum T₄.

In this study no patient had clinical or biochemical features of hyperthyroidism.

CONCLUSIONS

1. Thyroid hormone dysfunction occurs in 58% of the chronic renal failure patients.
2. Incidence of hypothyroidism is increased in patients with chronic renal failure.
3. Both clinical and biochemical parameters are essential to diagnose hypothyroidism in patients with CRF.
4. Excluding patients with hypothyroidism, T_3 level is low in 46% of the patients, T_4 level is low in 20% of the patients.
5. Number of patients with low T_3 and T_4 syndrome progressively increase with severity of renal failure.
6. Serum level of T_3 and T_4 has no correlation with the severity of renal failure.
7. Alteration in the values of T_3 and T_4 occurs as a part of body adaptations mechanism to conserve energy.

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PROFORMA

Name: Age: Sex: I.P.No:

Occupation: Address:

Past history:

HT: Y/N DM: Y/N Recent Surgery: Y/N

Drugs: Y/N Jaundice: Y/N

Other Systemic illness: Y/N

Menstrual and Obstetrical History:

General Examination:

1. Nourishment:
2. Pallor:
3. Hyper pigmentation:
4. Facial Puffiness:
5. Pedal edema:
6. Skin texture:
7. Thyroid swelling:
8. Vital signs:

Pulse: B.P:

Respiratory Rate: Temperature:

C.V.S.:

R.S.:

Abdomen:

C.N.S.:

Investigations:

1. Urine complete examination:

2. 24 hrs Urine Protein:

3. Blood:

Hb: gm/dl

Tc:

DC:

RBC:

Peripheral Smear:

4. Blood

Urea:

Creatinine:

Serum electrolytes: Na:

K:

Calcium:

Phosphorus:

Serum Cholesterol:

Serum Proteins

5. ECG:

6. Chest X- Ray

7. USG Abdomen

8. Thyroid Profile:

Serum triiodothyroxine:

Serum Thyroxine

Serum thyroid stimulating hormone

ABBREVIATIONS

CKD - Chronic Kidney Disease

DIT - Diiodotyrosine

ESRD - End stage renal disease

FT4 - Free Thyroxine

GFR - Glomerular Filtration Rate

MIT - Monoiodotyrosine

PTH - Parathyroid hormone

T3 - Triiodothyronine

T4 - Thyroxine

TRH - Thyrotropin Releasing Hormone

TSH - Thyroid Stimulating Hormone

TBG - Thyroxine Binding Globulin